REMARKS

The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 1, 3, 4 and 6-10 are pending in the application. Claims 1, 3, 4 and 6-10 have been rejected. Claims 4 and10 have been amended.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

In the Office Action, the Examiner rejected claims 4, 6 and 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner rejected Claims 4, 6 and 10 are under 35 U.S.C. §112, second paragraph, since the phrase "(a) dissolving haloperidol and biodegradable polymer consisting essentially of selected from the group [*sic*] in acetone" in Claim 4, is confusing because it is not made known by the claim language what the biodegradable polymer is consisting essentially of and what is being selected from the group consisting of. Likewise, the phrase (a) selects the biodegradable polymer from " polylactide or and lactide-co-glycolide," the use of and in that case is appropriate and it appears that the presence of "or" before the "and" is a typographical error.

Applicants respectfully disagree, the claims amendment entered in the 17 October 2007 request for continued examination, which has been entered, clearly crosses out the term objected to by the Examiner:

> "4. (Currently Amended) A method of producing an individual, surgically implantable implant which is surgically implanted underneath the skin of a patient for delivery of steady state concentrations of haloperidol to the patient for 5 months or more comprising: (a) dissolving haloperidol and a biodegradable polymer consisting essentially of ~~selected from the group consisting of~~ polylactide or ~~and~~ lactide-co-glycolide copolymer in acetone; (b) solvent casting the baloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and (c) molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations

of haloperidol to the patient for 5 months or more, and is removable following implantation into a patient in the event the patient exhibits unwanted side effects following implantation."

Making the previously presented claim read:

"A method of producing an individual, surgically implantable implant which is surgically implanted underneath the skin of a patient for delivery of steady state concentrations of haloperidol to the patient for 5 months or more comprising: (a) dissolving haloperidol and a biodegradable polymer consisting essentially of polylactide or lactide-co-glycolide copolymer in acetone; (b) solvent casting the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and (c) molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more, and is removable following implantation into a patient in the event the patient exhibits unwanted side effects following implantation."

As shown hereinabove, in view of the amendment entered in October 2007, there should be no confusion as to the biodegradable matrix comprising the implants described herein. Likewise, the claim makes it clear that the coordinating conjunction term to be used is "or" and not "and", which was crossed out in the entered amendment.

Accordingly, Applicants assert that claim 4 is definite under 35 U.S.C. § 112, second paragraph. Since claim 6, depend from amended independent claim 4, it contains all the limitations of independent claim 4 as amended and is therefore also proper under 35 U.S.C. § 112, second paragraph.

In addition, the Examiner rejected Claim 10, which depends from claim 7. Specifically, the Examiner asserts that it is unclear whether in claim 10, a different antipsychotic drug is further administered orally to the patient or it is the haloperidol that is further administered orally to the patient.

In response, Applicants amended claim 10 to recite:

"10. (Currently Amendment) The method of claim 7 further comprising administering to the patient another antipsychotic drug."

It was clearly the intent of the Applicants to refer to an additional antipsychotic drug administered with the removable implants of the invention. Support to that effect can be found on page 4, Para [0032] reciting: "Implants of the present invention can be used alone or combined with oral supplementation of haloperidol ***or another antipsychotic drugs for dynamic response to optimum medication levels***."[Emphasis added]

Accordingly, Applicants assert that claim 10 is definite under 35 U.S.C. § 112, second paragraph.

In view of the above, Applicants assert that claims 4, 6 and 10 are proper under 35 U.S.C. § 112, second paragraph and respectfully request that the Examiner remove the rejection.

35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1 and 3 under 35 U.S.C. § 103(a), as being unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212.

Specifically, the Examiner asserts that Cheng et al., which describes haloperidol-loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere (abstract), achieved a 10% haloperidol. Further, the Examiner asserts that the "Surgically implantable drug delivery" is in the preamble and represents the intended use of the delivery system while the body of the claim fully defines the claimed system. As the Examiner admits, the difference between the claims in the present Application and Cheng et al., is that the claims recite a range of 20-40% of haloperidol being fabricated into the polymer while Cheng uses 10%. However, asserts the Examiner Cheng et al., discloses a drug content of from 14.6 to 23.9%, which can supposedly be loaded onto the PLG microspheres and therefore, taking the teaching of Cheng et al., one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to formulate haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere in which the drug load is 10% or from 14.6 to 23.9%.

Applicants respectfully disagree.

As an initial matter, Cheng et al., fails to disclose each and every element in Applicants claim 1 as previously presented. Claim 1 recites: "A surgically implantable drug delivery system, comprising (a) a biodegradable polymer or copolymer, wherein said biodegradable polymer or copolymer consists essentially of polylactide or lactide-co-glycolide copolymer; and (b) 20 to 40% haloperidol fabricated into an individual, ***surgically implantable implant*** via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the ***individual, surgically implantable implant*** which is ***surgically implanted underneath the skin of a patient***, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation."[Emphasis added].

As shown, surgically implanting the systems disclosed in the Application is clearly not merely a part of the preamble. Cheng et al., refers to parenterally administered depot systems not surgical implants. Since the Cheng et al., reference refers to injectible depot microsphere of Haloperidol (as admitted by the Examiner in a subsequent rejection), it fails to anticipate each and every element of the claim and it therefore fails to provide a *prima facie* evidence of obviousness (MPEP 2143).

Moreover, there is no reasonable expectation of success in the use of the Cheng et al., reference for delivery of 20-40% Haloperidol.

With regard to the Examiner's assertion that Cheng et al., uses 10% and discloses a drug content of from 14.6 to 23.9%, Applicants respectfully disagree. As indicated in the Cheng et al., reference on page 208 (left column, last two sentences, first paragraph): "A 5mg/ml concentration Haloperidol in DCM solution containing 50 mg/ml PLG polymer was found to be the Maximum initial drug content for the preparation of haloperidol-loaded PLG microspheres ***without drug crystals*** dispersed in the final product. Hence, ***the maximum theoretical loading of haloperidol in PLG microspheres was around 10%.***" [Emphasis added].

Moreover, Cheng et al., admits in (Please Cite) that 10% haloperidol loading is only a theoretical limit.

Claim 1 as previously presented discloses 20-40% ACTUAL loading of Haloperidol, not THEORETICAL maximal loading of 10 %. In Cheng et al., the actual loading ranging between 0.74 to 3.07 % (See e.g. Table 2, page 208), representing an order of magnitude difference in the actual loading from the present Application. Moreover, contrary to the Examiner's assertion, Cheng et al., does not disclose loading of between 14.6 to 23.9% in PLG microspheres. Rather Cheng et al., discusses a different reference by Boidron-Celle et al., without any indication whether the drug in the carrier system is Haloperidol, or for that matter, what is the exact structure of the carrier composition. As a matter of fact, the 14.6 to 23.9% drug loading achieved by Boidron–Celle et al., (*See* e.g. J Pharm Pharmacol. 1995 Feb;47(2):108-14. javascript:PopUpMenu2_Set(Menu7602463);) was of 5-fluorouracil in anticancer treatment, where sustained release was obtained for 18 days only and even that was achieved using drug crystals.

Therefore, by limiting the theoretical loading of Haloperidol at 10%, Cheng et al., teaches away from the present invention and a person of ordinary skill in the art would not expect a loading of 20-40% Haloperidol to be theoretically possible, let alone actually achievable. Accordingly, Cheng et al., does not anticipate Claim 1 and claim 3 which depend directly therefrom.

Finally, there is no suggestion or motivation, either in the Cheng et al., reference or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of Cheng et al., for creating a removable drug delivery system.

As the inventors noted specifically for depot delivery systems (See page 1, Para 7-10):

"Pharmacological approaches to improved adherence include improving tolerability and efficacy of antipsychotic medication (Bustillo et al. Harv. Rev. Psychiatry 1999 6(5):229-40; Kane, J. Br. J. Psychiatry Suppl. 1999 37:26-9; Kasper, S. Int. Clin. Psychopharmacol. 1998 13 Suppl 3:S71-7; Mauskopf et al. J. Clin. Psychiatry 1999 60(Suppl 19):14-9) through development of new agents ***and administration of monthly depot preparations*** of existing agents.

Decreased rates of discontinuation were reported for a newer agent, olanzapine, than an older one (haloperidol) (Tran et al. J. Clin. Psychiatry 1997 Jun 58(5):205-11; Tran et al. J. Clin.

Psychiatry 1997 Jun 58(6):275). However, ***newer agents have been reported to have additional side effects*** including weight gain, sedation, drooling, Q-T prolongation and agranulocytosis (Campbell et al. Br. J. Clin. Pharmacol. 1999 47(1):13-22; Wetterling, T. and Mussigbrodt, H. E. J. Clin. psychopharmacol. 1999 19(4):316-21).

Monthly depot preparations have been reported as an effective means to decrease relapse and rehospitalization (Gerlach, J. Int. Clin. Psychopharmacol. 1995 9 Suppl 5:17-20). Treatment for noncompliant patients with depot formulations (Haldol-decanoate) is much less expensive per year than oral preparations of newer neuroleptics (risperidone; Galzer, W. M. and Ereshefsky, L. J. Clin. Psychiatry 1996 57(8):337-45). ***However, a 7-year study of depot medication found a significant number of patients fail to comply with monthly injections and discontinuation linked to relapse*** (Curson et al. Br. J. of Psychiatry 1985 146:469-74). Therefore, while depot medication improves adherence initially, many patients still become nonadherent (Weiden et al. Psychiatric Services 1995 46(10):1049-54).

In contrast, a surgically implantable preparation can last for many months, providing patients with symptomatic improvement and possibly delayed disease progression for periods of time never before possible. Additionally, in the event of unacceptable side effects, implants can be removed. This offers a degree of reversibility not presently available with depot formulations. Further, surgically implantable formulations can be employed as a safety net in combination with oral dosing to achieve adjustments as clinically indicated." [Emphasis added]

Being an injectable system, with limited duration of release (T_{50} of 55 days in Cheng et al.,), removability is impossible and the present invention specifically intends to overcome the shortcomings of a depot-based drug release system. Therefore, there is no suggestion or motivation, either in the Cheng reference or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of Cheng et al., for creating a removable drug delivery system with sustained release for 5 months or more as recited in Applicants claim 1.

In summary, the Cheng et al., reference is improperly cited, since a.) there is no suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; b.) there is no reasonable expectation of success in actually loading the microsphere with more than 10% Haloperidol;

and c.) the Cheng et al., reference fails to teach or suggest all the claim limitations including surgical implantation, 20-40% haloperidol actual loading and removability of the implant.

Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 1 and 3 under 35 U.S.C. § 103(a) in view of Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212.

In the Office Action, the Examiner rejected claims 1 and 7-10 under 35 U.S.C. § 103(a) as being unpatentable over Cheng et al, in view of view of Domb et al. ("Degradable Polymers for Site-Specific Drug Delivery," in polymers for Advanced Technologies, Vol. 3, pp. 279-292, 1992. Specifically, the Examiner asserts that Cheng et al., administers the haloperidol by injecting the composition as a depot. But, the Examiner alleges, implantation/implant reads on depot resulting from depot injections, and it is known to use degradable polymers to deliver drugs to target sites of interest ad described by Domb and carries the advantage that implants are used as site specific drug delivery routes.

Applicants respectfully disagree. First, Cheng et al., either alone or in combination, with Domb et al., fails to teach all claim elements of independent claims 1 and 7.

Cheng et al., is discussed above and that discussion applies here.

As mentioned above, Cheng does not disclose the 20-40% Haloperidol loading, the surgical implantation and the removability of the implant disclosed in the application's claims 1 and 7 and the Domb reference fails to cure that deficiency. Therefore the combined Cheng-Domb references do not teach all the claims' elements.

Moreover, there is no motivation to combine Cheng et al., and Domb et al., references. When, a proposed modification would render the prior art being modified such as in the case of Cheng et al., unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. The purpose of the disclosed subject matter in the Cheng et al., reference, is to overcome the oily depot systems that preceded the published reference. As noted on pages 204 and 211 of Cheng et al., the development of the formulation was to ameliorate the pain associated with intramuscular oily injection of depot delivery systems, without the typical drug burst associated with depot delivery systems.

Increasing the Haloperidol content beyond 15% as disclosed in the present application in Claims 1 and 7, would result in crystal formation in the Cheng et al., microspheres, changing the particle size, size distribution and actual drug content (See page 208), thereby affecting the desired release profile, making the microspheres unsatisfactory for their intended purpose. Therefore, there is no suggestion or motivation to modify the Cheng et al., reference to obtain the results described in the present application.

Likewise, the Domb et al reference is a general review article and the Examiner does not provide specific citation to the place in the article where there is the suggestion or motivation to modify drug loaded depot delivery systems, that are administered parenterarlly intramuscularly to subcutaneous implants.

Therefore neither Cheng et al., nor Domb et al., alone or in combination a.) anticipate the use of surgically implanted, removable implants containing 20-40% haloperidol; and b.) contain any suggestion or motivation to combine the references. Therefore, claims 1 and 7 are patentable over Cheng et al., in view of Domb et al. Since claims 8-10 depend directly or indirectly from one of independent claims 1 or 7, they contain all the limitations of these independent claims and are likewise patentable.

Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 1 and 7-10 under 35 U.S.C. § 103(a) as unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of Domb et al. ("Degradable Polymers for Site-Specific Drug Delivery," in polymers for Advanced Technologies, Vol. 3, pp. 279-292, 1992.

In the Office Action, the Examiner rejected Claims 4 and 6 as being unpatentable over Cheng et al., in view of Sidman (US 4,450,150, the '150 Patent). According to the Examiner, Cheng prepares the haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere by solvent evaporation (section 2.2). Cheng admittedly, does not cast the haloperidol dissolved in the solvent in a mold so that Cheng differs from the invention by not

molding the haloperidol-polymer solution. However, it is known that implants that deliver drugs to target sites are molded by compressing or injecting the drug formulation as disclosed by Sidman (column 9, lines 8-12; column 10, lines 51-52; column 18, line 29) making the present Application obvious.

In response, Applicants amended independent claim 4 to recite a step of dissolving between about 20% and 40% haloperidol and a biodegradable polymer consisting essentially of polylactide or lactide-co-glycolide copolymer in acetone.

Cheng et al., is discussed above and that discussion applies here.

As mentioned above, Cheng does not disclose the 20-40% Haloperidol loading, the surgical implantation and the removability of the implant disclosed in the application's independent claim 4 as amended and the '150 Patent fails to cure that deficiency. Therefore the combined Cheng-'150 Patent references do not teach all the claims' elements.

An obviousness rejection requires a teaching or a suggestion by the relied upon prior art of all the elements of a claim (M.P.E.P. §2142). Since Cheng et al., or the '150 Patent, alone or in combination, do not teach or suggest all the elements of independent claim 4 as amended, the Examiner fails to establish a *prima facie* showing that Cheng et al., or the '150 Patent, alone or in combination, teach or suggest every feature of claims 4 as amended.

Accordingly, Applicants respectfully request that the examiner remove the rejection of claims 1 and 7-10 under 35 U.S.C. § 103(a) as unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of US Patent No. 4,450,150 to Sidman.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

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